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Looking Beyond *BRCA1/2* Among Breast Cancer Patients

BY BRANDON MAY

In a new study from the University of Pennsylvania in Philadelphia, researchers have found that patients with breast cancer and a second primary cancer have double the risk of having inherited germline variants in genes other than *BRCA1/2*, particularly *TP53* and *MSH6*, when compared with patients with a single breast cancer. Findings from this study were presented at the 2018 ASCO Annual Meeting in Chicago (*J Clin Oncol* 36, 2018 [suppl; abstr 1503]).

According to the investigators, this study highlights the importance of using a multiple genetic testing panel in risk assessment and prediction of patients who have experienced multiple primary cancers. Kara N. Maxwell, MD, PhD, the leading study author and Assistant Professor of Medicine at the University of Pennsylvania Perelman School of Medicine, Philadelphia, who presented the

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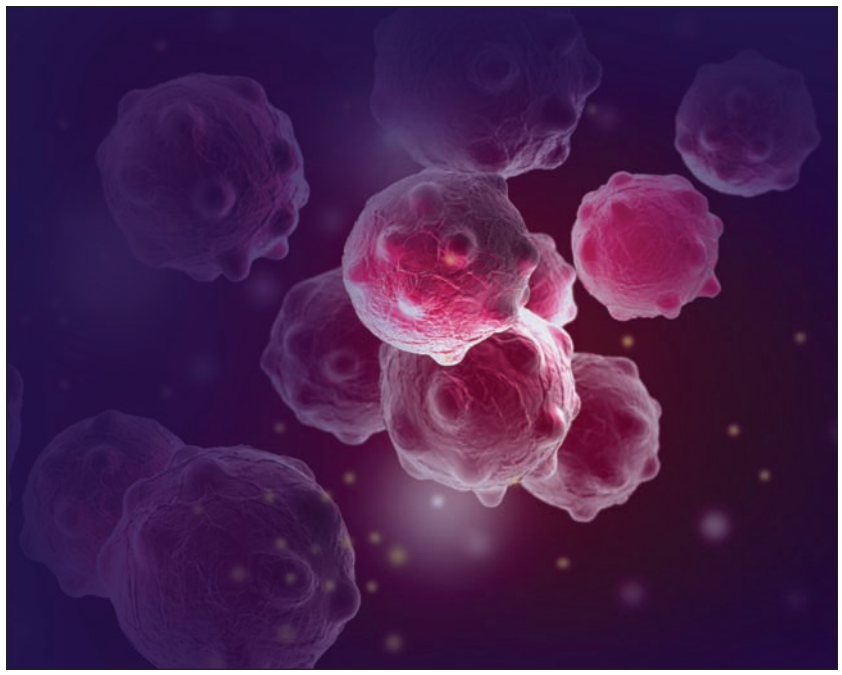

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Evaluating CAR-T Therapy in Patients With Refractory B-Cell Lymphomas

BY RICHARD SIMONEAUX

When patients are diagnosed with large B-cell lymphomas, such as transformed follicular lymphoma, primary mediastinal B-cell lymphoma, or diffuse large B-cell lymphoma (DLBCL), they are typically prescribed a regimen of combination chemoimmunotherapy. Those patients with chemotherapy-susceptible disease who experience a relapse often receive high-dose chemotherapy and subsequent autologous stem cell transplantation (ASCT). Those patients experiencing either resistance to primary or salvage setting chemoimmunotherapy or a post-ASCT relapse have extremely poor prognoses.

CME Article

One potential therapy for this patient subpopulation is the autologous chimeric antigen receptor T-cell therapy (CAR-T) axicabtagene ciloleucel (axi-cel). This

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The Role of Novel Antibody Strategies in Relapsed/Refractory Multiple Myeloma

BY CATLIN NALLEY

Based on findings from recent randomized controlled trials next-generation proteasome inhibitors (carfilzomib and ixazomib), a next-generation immunomodulatory agent (pomalidomide), and monoclonal antibodies (elotuzumab and daratumumab) have been approved for relapsed/refractory multiple myeloma (*Leukemia* 2018; doi:10.1038/leu.2017.329).

However, despite advances, management of the disease still proves challenging.

During the 2018 ASCO Annual Meeting, Rachid Baz, MD, Senior Member, Department of Malignant Hematology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla., led a discussion on novel antibody strategies in this patient population.

Elotuzumab in Combination

Elotuzumab is an approved monoclonal antibody that enhances the activity of lenalidomide and bortezomib in multiple myeloma. Researchers recently studied the agent in combination with pomalidomide, bortezomib, and dexamethasone (elo-PVD) in relapsed/refractory multiple myeloma (*J Clin Oncol* 2018;36(suppl; abstr 8012)).

"Elotuzumab is a monoclonal antibody targeting SLAMF7 and it doesn't have robust single-agent activity in relapsed/refractory disease," noted Baz during the presentation at ASCO. "However, in combination with lenalidomide and dexamethasone, it

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Evaluating CAR-T Therapy in Patients With Refractory B-Cell Lymphomas

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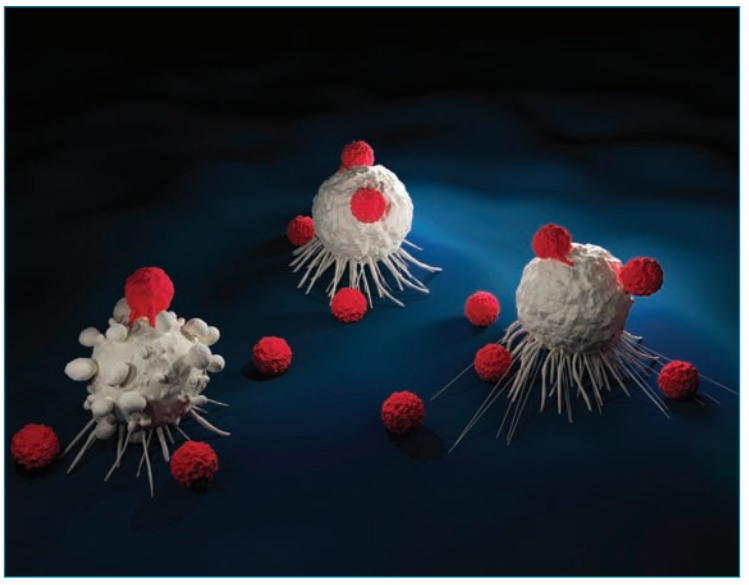
treatment, which utilizes the patient's own genetically modified T cells, targets those cells overexpressing cluster of differentiation 19 (CD19).

To evaluate this potentially useful therapy in patients with B-cell lymphomas (e.g., DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma), the multi-center ZUMA-1 trial (NCT02348216) was initiated. Recently, results from the primary analysis of the phase II portion of the trial were reported by a group of clinicians, including Sattva Neelapu, MD, Professor, Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas, MD Anderson Cancer Center, Houston (*N Engl J Med* 2017;377:2531-2544).

Regarding these results, Neelapu noted: "Of the 111 patients enrolled in this trial, axi-cel modified T cells were successfully manufactured for 110 (99%) and then administered to 101 (91%). At the time of primary analysis for the phase II portion of the study, the objective response rate (ORR) was 82 percent, with a total of 54 percent of the participants displaying a complete response (CR)."

Background

The axi-cel therapy utilizes the patient's isolated white blood cells, which were genetically modified using an NCI-developed CAR construct (*Leuk Lymphoma* 2017; doi:10.1080/10428194.2017.1387905).



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When asked to describe the nature of the modifications to the T cells, Neelapu replied, "The genetic engineering redirects the specificity of the T cells to target the tumor cells. The CAR construct that is introduced into the isolated T cells, typically via viral vector delivery, has two major parts: 1) an extracellular portion consisting of an antibody that binds to the CD19 protein expressed on B-cell lymphomas, and 2) an intracellular portion consisting of CD3 zeta chain and CD28 to provide the activation signal to the T cells when the extracellular portion recognizes its target on the tumor cell."

Once ex vivo expansion of the modified T cells has occurred, they are then returned to patients via IV infusion. In the interim between leukapheresis and CAR-T administration, patients received lymphodepletion-inducing conditioning chemotherapy, which creates within the patient an optimal environment for CAR T-cell expansion and antitumor activity.

"Upon activation in vivo," he stated, "the T cells produce cytokines, perforin, and granzymes that mediate the killing of the tumor cells."

The phase I portion of the ZUMA-1 multicenter study, which included seven patients with refractory large B-cell lymphoma, showed that axi-cel could be centrally manufactured and safely administered. Five patients exhibited a response to axi-cel therapy, of which, four were complete responses. Additionally, three of these patients maintained an ongoing CR after 1 year.

In October 2017, largely based on the results obtained in the phase II portion of the ZUMA-1 study, the FDA granted approval for the use of axi-cel in adult patients with large B-cell lymphoma (including DLBCL, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma) who have not responded to or who have relapsed after at least two prior therapies. However, this axi-cel approval did not extend to the treatment of primary CNS-based lymphomas.

Methodology

Participation in this study was limited to those patients having refractory (i.e., displaying progressive disease (PD) or stable disease as a best response to the most recent chemotherapy regimen or PD or relapse within 12 months after ASCT), histologically confirmed large B-cell lymphomas. Retrospective diagnosis confirmation was centrally performed.

> "The CAR-T therapy could be manufactured for 99 percent of the patients even though these patients were heavily pre-treated with multiple chemotherapy regimens."

After isolation of the patient's T cells, they were subjected to the axi-cel manufacturing process. Patients received a low-dose conditioning chemotherapy (30 mg/m^2 fludarabine, QD and 500 mg/m^2 cyclophosphamide, QD) on days -5, -4, and -3 before IV delivery (single infusion) of axi-cel (target dose of 2 million engineered T cells per kg of body weight) on day 0. No bridging chemotherapy was permitted between leukapheresis and axi-cel infusion. Retreatment was permitted for those patients who experienced progression more than 3 months after initial axi-cel infusion.

The primary objective in this study was the investigator-assessed ORR, defined as the combined rates of those patients displaying CR and partial response. Among the secondary endpoints were progression-free survival, duration of response (DOR), adverse events (AEs), blood levels of CAR-T cells and cytokines. The data cutoff date was Aug. 11, 2017, which afforded a median follow-up period of 15.4 months.

Study Results

Between November 2015 and September 2016, 111 patients were enrolled in this study at 22 different treatment centers. Of these patients, 110 had successful axi-cel manufacturing, with delivery being performed for 101 (those actually receiving axi-cel constituted the modified intention-to-treat population). The following reasons were noted for the 10 patients not receiving axi-cel injection: AEs (4); non-measureable disease before conditioning chemotherapy (2); unsuccessful axi-cel manufacturing (1); death from disease progression (1); sepsis arising between conditioning chemotherapy and axi-cel infusion (1); death between conditioning chemotherapy and axi-cel infusion from a host of factors possibly including tumor lysis syndrome, gastrointestinal bleeding, and disease progression (1).

The ORR obtained in the primary analysis for the 101 patients receiving axi-cel was 82 percent (95% CI: 73–89%), while the CR rate was 54 percent. The median time of response was 1.0 month (range: 0.8–6.0 months), while the median DOR was 8.1 months (95% CI: 3.3 month–not estimable).

"Response rates were consistent across key covariates, including age, disease stage, International Prognostic Index score at enrollment, presence or absence of bulky disease, cell-of-origin subtype, and tocilizumab or glucocorticoid use," Neelapu noted.

Consistent responses were noted in those patients having primary refractory disease (n=26, ORR-88%) as well as in those having a history of ASCT (n=21, ORR-76%). "The response rates did not appear to be influenced by biologic covariates, e.g., the prevalence and intensity of CD19 expression, or by product characteristics, such as the CD4:CD8 cell ratio and T-cell phenotypes," he stated.

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The most commonly noted AEs of any grade were pyrexia (85%), neutropenia (84%), and anemia (66%). For AEs of grade 3 or higher, the most common were neutropenia (78%), anemia (43%), and thrombocytopenia (38%). A potentially serious complication in CAR-T patients is cytokine release syndrome (CRS). This condition was observed in 93 percent of the patients; however, the majority of these were considered low grade (i.e., grade 1 or 2). The breakdown by grade for CRS was as follows: grade 1–37 percent; grade 2–44 percent; grade 3–9 percent; grade 4–3 percent; grade 5–1 percent.

The highest levels of CAR T cells in the peripheral blood were observed within 14 days after axi-cel administration and were detectable in most patients at 180 days post-infusion. Detectable blood-based CAR T-cell levels were noted in three patients who had ongoing complete remission at 24 months.

"In vivo CAR T-cell expansion was significantly associated with response ($P<0.001$)," Neelapu said, further adding, "with an area under the curve within the first 28 days after infusion that was 5.4-fold greater among responding patients compared to those who were non-responding."

Discussion

When asked what he felt the most surprising findings were for this study, Neelapu replied, "I think the high overall and complete response rates of 82 percent and 58 percent, respectively, for the updated analysis (including the results obtained for both the phase I and phase II portions of ZUMA-1) and the durability of the responses in a significant proportion of patients with the appearance of a plateau in the progression-free survival curve around the 6-month time point was unexpected in this chemorefractory patient population.

"What was also remarkable is that the CAR-T therapy could be manufactured for 99 percent of the patients even though these patients were heavily pre-treated with multiple chemotherapy regimens."

Concerning the AEs observed in this trial, he noted, "There are two major toxicities observed with CAR-T therapy. The most common is CRS, which typically manifests with fever, malaise, and loss of appetite, but in more severe cases may lead to multiple organ dysfunction. Most patients only have low-grade CRS, which is typically managed by mostly supportive care, whereas severe CRS is treated with tocilizumab, an anti-IL-6 receptor antibody, with or without corticosteroids in addition to supportive care."

The second most common toxicity," he stated, "is neurological toxicity that is usually low-grade with confusion, agitation, somnolence, and/or aphasia. However, in severe cases, seizures may occur; low-grade neurological toxicity is managed with supportive care and corticosteroids are used for severe toxicity."

When discussing the trial endpoints, Neelapu noted, "The study met its primary endpoint for overall response rate with a P value of <0.0001 compared with a 20 percent historical response rate in this patient population. The ZUMA-1 trial is the first multicenter trial of CD19 CAR-T therapy that has shown significant efficacy of this approach in patients with relapsed or refractory large B-cell lymphoma.

"At a median follow-up of 15.4 months," he stated, "forty-two percent of the patients remain in remission after a single infusion of this treatment; CRS and neurological toxicities are the most common toxicities but are generally reversible. The results obtained in this trial led to FDA approval of axi-cel CD19 CAR-T therapy in October 2017.

"Consistent responses were noted across key clinical covariates tested," Neelapu noted, "including patients with low and high International Prognostic Index, ABC and GCB variants of diffuse large B-cell lymphoma, and patients with bulky or extra nodal disease. Patients with complete response had a much better chance of durable response than those with partial response or stable disease; the response to CAR-T therapy was associated with peak CAR T-cell expansion in patients post-infusion."

When queried about potential weaknesses of this study, Neelapu replied, "One limitation of our study is the lack of a planned, detailed analysis of molecular and cytogenetic characteristics. Prospective data are needed on the influence of disease biology, such as double- and triple-hit lymphomas, on outcomes with CAR T-cell therapy."

Regarding the timing of the axi-cel procedure, he commented, "To be successful, a personalized cell therapy must be delivered in a safe and timely manner. The short 17-day median turnaround time was critical for these refractory large B-cell lymphoma patients, as they generally have rapidly growing disease."

Assessing this critical point, Neelapu said, "In this study, we confirmed the feasibility and reliability of centralized manufacturing and coordination of leukapheresis procedures and shipping from multiple centers across the country. We found that axi-cel could be administered safely at medical facilities that perform transplantation, even if such centers had no prior experience in CAR T-cell therapy.

"This therapy is now being evaluated in earlier stages of the disease process," he continued. "A randomized trial has been initiated to directly compare the efficacy of CAR-T therapy with ASCT in patients with large B-cell lymphoma at first relapse. In addition, this therapy is also being evaluated in other lymphoma subtypes including relapsed or refractory indolent B-cell lymphomas and mantle cell lymphoma. To further improve the efficacy of this treatment, the CAR-T therapy is being combined with immune checkpoint inhibitors." OT

Richard Simoneaux is a contributing writer.

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Learning Objectives for This Month's CME Activity: After participating in this CME activity, readers should be better able to: 1. Analyze the results of the Phase 2 trial of axicabtagene ciloleucel (axi-cel) for patients experiencing either resistance to primary or salvage-setting chemoimmunotherapy, or a post-ASCT relapse. 2. Assess implications for future research avenues and applications of this treatment.